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Chemotherapy-Induced Immunosuppression

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Chemotherapeutic agents are used widely in clinical medicine for the treatment of conditions where diminution of the host immune response is a goal. The clinical use of immunosuppression is indicated for immunologically mediated disease, lymphoproliferative diseases, and prevention of graft rejection. Five categories of agents are useful for these purposes; they are ionizing irradiation, corticosteroids, biological alkylating agents, antilymphocyte sera and antimetabolites. While the specific molecular action of many of these drugs is known, how they affect cellular events in immune responses is less clear. One of the unfortunate sequelae of chemotherapy induced immunosuppression is an increased susceptibility of the host to opportunistic pathogens or malignancies.

Specific methods are described for monitoring the various parameters of both humoral and cellular immunity.

Studies of immunologic function in lymphoma patients and cardiac transplant patients treated with immunosuppressive drugs have shown specific defects in cell mediated immunity to herpes viruses which may relate to their increased susceptibility to infection by these agents.

Immunosuppressive Agents Used in Clinical Medicine

The use of immunosuppressive drugs in clinical medicine is necessary to diminish the immune response to a point where responses to undesirable foreign antigens are eliminated. This state of chemically induced immunologic unresponsiveness may have undesirable features, for example placing the host at risk of infection by a wide variety of opportunistic agents. This review will focus on three major areas: first, a broad review of immunosuppressive agents available in clinical medicine and clinical situations in which they are useful. Second, specific laboratory methods for assessing immunity will be emphasized. Last, model systems for studying the effects of immunosuppression will be analyzed.

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A battery of immunosuppressive agents is available for use in clinical medicine. These are detailed in Table 1 along with examples of each category.

Table 1. Immunosuppressive agents available in clinical medicine.

Agent	Example
Ionizing irradiation	Whole body irradiation Extracorporeal irradiation
Corticosteroids	Prednisone
Biological alkylating agents	Nitrogen mustards Cyclophosphamide *Chlorambucil, melphalan*
Lymphocyte depletion by thoracic duct drainage or antilympocyte serum	Antilymphocyte sera
Antimetabolites	
Antibiotics	Azaserine Mitomycin C Actinomycins Chloramphenicol
Purine, pyrimidine antagonists	6-MP, azathioprine Cytosine arabinoside
Folate antagonists	Methotrexate
Alkaloids	*Colchicine*

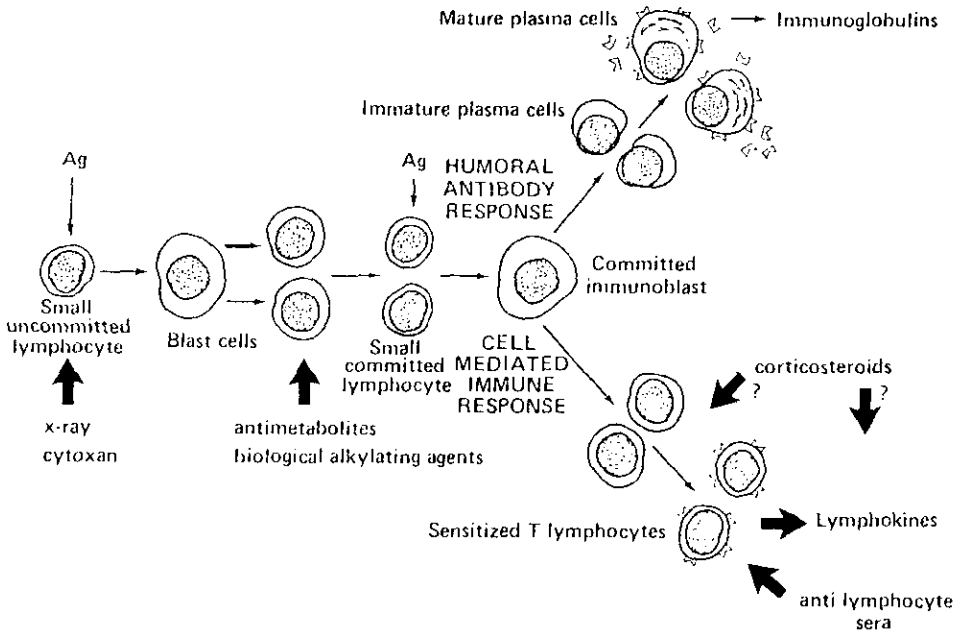

FIGURE 1. Schematic representation of stages in the immune response.

In general, these forms of immunosuppression are nonspecific and lead to diminution of response to a wide variety of agents. While methods of induction of unresponsiveness to specific antigens are available, they generally utilize either specific antibody or antigen. This area has been treated in detail in excellent reviews edited by Talmage and associates (*1*) and will not be considered here.

The modes of action of most immunosuppressive agents at the cellular level are complex and far from being clear at this point. Schematically, the events in an immune response may be divided into "inductive" and "productive" phases. The "inductive" phase involves the interaction of antigen with small lymphocytes. The "productive" stage involves steps resulting in the proliferation of stimulated cells with the eventual elaboration of products, for example, antibody for humoral immunity or sensitized T-lymphocyte and lymphokines for cell-mediated immunity. Most lines of evidence suggest that many immunosuppressive agents act mainly by impairing the reproductive capacity of immunologically competent or active cells. This may occur at multiple points in the cell cycle. Figure 1 schematically represents stages in the immune response culminating in both humoral and cellular immune responses. Irradiation at sublethal doses of 300 to 500 rads has variable effects on immune responses. Its primary site of action is probably at the level of destruction of the small lymphocyte population which is the precursor to events in immune proliferation. Cytotoxic drugs, for example antimetabolites and biological alkylating agents, act by interfering primarily with rapidly dividing cells. Alkylating agents will cross-link DNA strands. One exception is cytoxan, which may act by interfering with antibody at the stage of induction. Antilymphocyte sera are obtained from animals immunized with human lymphocytes and their main action appears to be on cell mediated immunity rather than antibody production. Corticosteroids are used primarily as anti-inflammatory agents, their main effect being stabilization of liposomal membranes within phagocytic cells. However, lympholytic activities as well as effects on T-cell–macrophage interaction have been ascribed to this group of drugs.

In general, nonspecific immunosuppressants are more effective at blocking the primary as compared to secondary or "anamnestic" immune response.

The use in clinical medicine of chemotherapeutic agents with immunosuppressive activity is directed at alleviating immunologically mediated disease, lymphoproliferative diseases and prevention of graft rejections following organ transplantation. Some examples of agents useful in these respects are shown in Table 2. However, prolonged immunosuppression is dangerous: not only are the agents highly toxic for various cells but their use is associated with increased susceptibility to various infections (Table 3) and to secondary malignancies. Particularly disturbing is the increased frequency of cancer in kidney allograft recipients. Suppres-

Table 2. Clinical uses of immunosuppression.

Condition	Example	Agent
Immunologically mediated disease		
Exogenous antigens	Allergy	steroids
Homologous antigens	Rh isoimmunization	Anti Rh_0 globulin
Autologous antigens	Autoimmune disease	Steroids
		Antimetabolites
Lymphoproliferative diseases	Multiple myeloma	Steroids
	Hodgkin's disease	*X-ray*
	Leukemia	Antimetabolites
Transplantation	Cardiac and renal transplants	Antilymphocyte serum
		Steroids
		Antimetabolites

Table 3. Infections associated with chemotherapy-induced immune suppression.

Viral
Herpesvirus infections, e.g., zoster, cytomegalovirus, Epstein-Barr
Viral vaccines, e.g., vaccinia
Bacterial
Gram-negative organisms
Staphylococcus aureus
Fungal/yeast
Aspergillus
Candida
Malignancies of unknown etiology
Tumors in homograft recipients on immunosuppression
Second and third malignancies in leukemia or lymphoma patients on cytotoxic therapy, particularly with biological alkylating agents.
Carcinomas in congenital immunodeficiencies

Table 4. Assessment of humoral immune functions.

Quantitation of serum immunoglobulins
Radial immunodiffusion
Serum electrophoresis
Immunoelectrophoresis
Quantitation of specific antibody
Agglutination
CF
RIA
ELISA
Specific antibody responses after immunization
B-cell quantitation by immunofluorescence and transformation response to mitogens PWM

Table 5. Assessment of cellular immune function.

Neutrophils
Quantitation
Phagocytosis: Nitroblue tetrazolium reduction
Skin test for delayed hypersensitivity to specific antigens, e.g., TB
T-lymphocytes
Quantitation: rosettes
Activation:
Transformation or DNA synthesis after mitogen, e.g., PHA or specific antigen stimulation
Lymphokines, e.g., migration inhibition factor, interferon
HLA restricted cytotoxicity

sion of cell-mediated rather than humoral immunity is thought to be primarily responsible, because the most effective antitumor responses are believed to be cell-mediated.

Specific Methods for Assessment of Immunity

Because of the known immunosuppressive action of many drugs used in clinical medicine, it is becoming of increasing importance to monitor immunologic parameters during therapy. Because immune function can be conveniently compartmentalized as either "humoral" or "cellular," it is operationally possible to assess functions in these respects. However, it must be emphasized that because of the interdependent nature of all immunologic responses, failure to detect reactivity at one level does not necessarily represent a primary site of action of a particular drug or drugs. Tables 4 and 5 list some specific methods that are useful in evaluating both humoral and cellular immunity. More detailed descriptions of these currently used methodologies are given elsewhere (*2*).

Model Systems for Studying Effects of Immunosuppressive Drugs in Patient Populations

At Stanford University Medical Center, there are two large populations of immunosuppressed patients. Patients are treated for Hodgkin's dis-

ease, as well as other lymphoid tumors, by irradiation and chemotherapy. Additionally, cardiac transplants have been performed at Stanford, and to reduce risk of graft rejection immunosuppression must be used in this group. Because of the frequent occurrence of infectious diseases in these two patient populations, we have instituted a program of prospective immunologic monitoring in order to attempt to identify those functions which may be useful prognostic indications of serious disease.

Herpes zoster, caused by varicella-zoster virus (VZ) in the treated lymphoma patients, for example Hodgkin's disease, is a recurrent and sometimes life-threatening occurrence. The incidence of herpes zoster in this particular patient group has been found to be higher than that among patients with solid tumors (*3*). The immunologic characteristics of Hodgkin's disease which may predispose to VZ infection include loss of pre-existing delayed hypersensitivity by skin testing as well as a loss of ability to acquire new hypersensitivities. Lymphopenia is present, but antibody formation is impaired only in advanced stages, beyond the period when zoster is most frequent. Among the patients with zoster, a significant number will develop disseminated disease superimposed upon the initial segmented lesion associated characteristically with a particular dermatome. Therefore, two specific problems probably related to deficient cell mediated immunity exist in this patient population: first, an increased risk of initial VZ disease and second, with disease occurrence, an increased frequency of dissemination.

Studies in our laboratory have focused on two parameters of cell-mediated immune function: lymphocyte transformation and interferon in responses to specific herpesviral antigens. Our studies have shown that lymphocyte transformation in this system represents a monocyte-dependent T-lymphocyte response, while B-lymphocytes, with the help of monocytes, produce interferon (*4*). T-lymphocyte transformation is immune-specific, in that only lymphocytes from individuals with serologic evidence of prior exposure will respond *in vitro* with increased DNA synthesis. B-lymphocyte interferon is augmented by herpesvirus disease, but can also be produced by lymphocytes from nonimmune individuals (*5*). Because of the recognized defect in cell-mediated immunity in patients with Hodgkin's disease, we used these two parameters of immunocompetent cell function to assess specific responses *in vitro* to VZ antigen.

In vitro lymphocyte responses to VZ antigen in lymphoma patients, untreated or in remission, were compared with those of normal individuals. The untreated lymphoma patients showed significantly lower responses than other populations tested, including normals with histories of chicken pox or recent zoster and lymphoma patients in remission. The lymphocyte interferon response was found to be lower in both untreated and lymphoma patients in remission as compared to normals (*6*). These defects were found to be specific for VZ, since responses in both lymphoma patient groups to herpes simplex antigen were comparable to those of normals. Prospective studies in 86 lymphoma patients analyzing the effect of the first 16 month's therapy upon lymphocyte functions to specific herpes viruses showed that more than 50% of the cases of zoster occurred in patients treated with both radiation and chemotherapy. The increased frequency in this group was accompanied by a specific defect in lymphocyte transformation to VZ antigen which persisted during the observation period (*7*). These studies also showed that the responses to nonspecific mitogens and T-cell numbers recovered to the range of normal individuals before responses to specific herpes viral antigens.

In the cardiac transplant population, CMV infections occur almost universally with varying manifestations. Some of these clinical findings include unexplained fever, pneumonitis, hepatitis, leukopenia and retinitis in the late period after transplant. The presence of antibody may not protect from shedding virus in throat or urine for prolonged periods or from destructive pathologic lesions. In cardiac transplant patients, defects in both lymphocyte transformation and interferon are present during the period of greatest risk of CMV, a finding similar to that for herpes zoster susceptibility in the lymphoma patients (*8*).

New forms of herpes zoster have been recently described in which unusually prolonged zoster was observed in patients treated with high doses of immunosuppressive chemotherapy (*9*). Usually a self-limiting disease, cases of zoster persisted in this group for as long as 6 months. Reduction of immunosuppressive therapy appeared to initiate resolution of zoster lesions and halt dissemination. Mechanism of this prolonged form of herpes zoster may relate to depressed cell mediated immunity in these hosts, since depression in T-lymphocytes was a goal of therapy in the patients studied. These studies suggest that small reductions or short term withholding of immunosuppressive drugs may be sufficient to allow resolution of chronic lesions.

Despite the obvious clinical value of immunosuppression, the use of such drugs must be evaluated both in terms of positive benefits and nega-

tive effects. Better understanding of specific immunosuppressive effects will allow their use with minimal adverse consequences.

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